REMARKS/ARGUMENTS

In response to the Office Action of March 10, 2005, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claims 1, 39 and 44-46 have been amended. Claims 2-38 were cancelled in a previous response (filed on January 10, 2005). Claims 39-46 are withdrawn from consideration. It is understood that claims 39-46, drawn to the non-elected invention, will remain pending, albeit withdrawn from prosecution on the merits at this time. If the examined claim of the Group I invention is deemed to be allowable, rejoinder of the remaining claims (39-46) in accordance with the decision in *In re Ochiai* is respectfully requested; since the remaining claims (39-46) are limited to the use of the biopolymer marker of claim 1 (the examined claim of the elected Group I invention).

Claim 1 is under examination. Claims 1 and 39-46 remain pending in the instant application.

No new matter has been added by the amendments to the specification made herein.

In the "Background of the Invention" section a punctuation

error was corrected at page 1, line 23.

The description of the reference at page 5 has been amended to correct a typographical error in the international application number. The corresponding international publication number has also been added.

The "Description of the Figures" section has been amended to add sequence identification numbers and to clearly indicate that Figures 2 and 3 show the mass spectrum profiles of the disclosed biopolymer markers.

Several protocols at pages 40-45 have been amended to properly identify trademark names (SEPHAROSE, TRITON, TRIS and EPPENDORF). The protocol titles at page 41 (lines 6 and 20), page 42 (line 12) and page 43 (lines 3 and 16) were underlined in the original disclosure and, with the exception of the term "SEPHAROSE" at page 41, line 20 and page 42, line 12, do not indicate text amended herein.

The paragraph at page 46 was amended for consistency of language and to correct grammatical errors.

In the "Detailed Description" section, the term "cerebrospinal fluid" has been added to define the abbreviation "CSF" at page 49, line 13 in order to provide explicit support for cerebrospinal fluid as recited in claim 41. "CSF" is a well known abbreviation for cerebrospinal fluid in the biochemical art. A typographical

error within the same paragraph has also been amended (skill replaced skilled).

The abstract has been amended to remove the legal phraseology ("said").

No new matter has been added by the amendments to the claims made herein.

Claim 1 has been amended to explicitly claim the biopolymer marker (SEQ ID NO:2). The term "biopolymer marker" is used throughout the specification as originally filed, see, for example, page 1, line 8.

Claim 39 has been amended to clearly disclose the relationship between the presence of the claimed biopolymer marker (SEQ ID NO:2) and insulin resistance. Claim 39 has also been amended to explicitly indicate how the presence of the claimed biopolymer marker is determined from mass spectrum profiles. The changes to claim 39 find basis throughout the specification as originally filed, see, for example, page 35, lines 14-18, page 46, lines 4-15 and Figures 1 and 3.

Claim 44 has been amended to correspond with the biopolymer marker of claim 1 (as amended herein). Support for various types of kits can be found in the original disclosure, see for example, page 36, lines 9-12 and page 47, line 11 to page 48, line 20. Claim 44 was also amended to correct a grammatical error(an replaced

and).

Claims 45 and 46 have been amended to provide proper antecedent basis for the term "kit" in claim 44 (as amended herein).

Restriction

The Examiner has determined that the requirement for restriction is still proper and therefore has made the requirement final.

Applicants have claimed the biopolymer markers (SEQ ID NOS:1-5)in a Markush-type grouping indicating that SEQ ID NOS:1-5 are alternatively usable (MPEP 803.02). In contrast to Applicants' presentation of SEQ ID NOS:1-5 in a Markush-type grouping, the Sequence Election Requirement presents each of SEQ ID NOS:1-5 as unrelated, patentably distinct sequences, thus introducing a contradiction into the prosecution history. Such contradictions can potentially diminish the value of any patent that may issue from the instant application. For example, since Applicants are required to elect a Group (and a single sequence) for prosecution on the merits, one reading the prosecution history may incorrectly assume that Applicants admit that the biopolymer markers of SEQ ID NOS:1-5 are separate and distinct inventions.

Request for Rejoining of Claims

Considering that claims 39-46 are limited to the use of SEQ ID NO:2 a search of these claims would encompass this specific peptide. The instant application is related in claim format to several other applications, both pending and issued, of which serial number 09/846,352 is exemplary. In an effort to maintain equivalent scope in all of these applications, Applicants respectfully request that the Examiner consider rejoining claims 39-46 in the instant application, which are currently drawn to non-elected Groups, with claim 1 of the elected Group under the decision in *In re Ochiai* (MPEP 2116.01), upon the Examiner's determination that claim 1 of the elected invention is allowable and in light of the overlapping search. If the biopolymer marker peptide of SEQ ID NO:2 is found to be novel, methods and kits limited to its use should also be found novel.

Oath/Declaration

A new oath or declaration has been required by the Examiner because while the original oath filed on February 12, 2002 contains the signature of Dr. John Marshall (inventor 2), the date of signature is omitted.

A new declaration, which has been properly executed and dated, is filed herewith.

Objection to the Specification

The Examiner points out guidelines for the proper language and format of an abstract of a patent application and objects to the abstract of the instant application as it recites the legal phraseology "said".

The abstract of the instant application has been amended herein to remove the legal phraseology "said".

Applicants have now addressed the Examiner's objection and respectfully request that the objection to the specification be withdrawn.

Rejection under 35 USC 112, first paragraph

Claim 1, as presented on January 10, 2005, stands rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner asserts that the claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants respectfully disagree with the Examiner's assertion.

Although Applicants believe that the instant specification,

as originally filed, fully supports the claim that an isolated peptide consisting of SEQ ID NO:2 is diagnostic for insulin resistance, in the interest of compact, efficient prosecution, Applicants have removed the term "diagnostic" from the claims and note that the isolated peptide consisting of SEQ ID NO:2 is linked to insulin resistance.

According to the web site dictionary.com the term "linked" refers to the condition of being associated with or connected to (see attached document as accessed from the internet; reference 1). The instant specification fully supports a connection and/or an association of the claimed peptide with insulin resistance. The instant specification states at page 35, lines 14-18 that an objective of the invention is to evaluate samples containing a plurality of biopolymers for the presence of disease specific biopolymer marker sequences which evidence a link to at least one specific disease state.

The "test of enablement" is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the prior art without undue experimentation (see MPEP 2164.01).

Furthermore, the decision in *In re Brandstadter* (179 USPQ 286; MPEP 2164.05) has established that the evidence provided by applicant (to overcome an enablement rejection) need not be

conclusive but merely convincing to one of skill in the art.

Applicants respectfully submit that the instant specification provides sufficient evidence to convince one of skill in the art that the claimed peptide (SEQ ID NO:2) is linked and/or associated with insulin resistance.

Claim 1 has been amended to specifically recite an isolated peptide consisting of SEQ ID NO:2, a peptide which the instant specification identifies as related to insulin resistance. Claim 1, as amended herein, does not recite that the claimed isolated peptide is diagnostic for insulin resistance, nor does it recite that the claimed isolated peptide is related to insulin resistance, even though Applicants believe that the specification, as originally filed, fully supports both of these recitations. Furthermore, the phrase "consisting of" is closed language and excludes any element, step or ingredient not specified in the claims (see MPEP 2111.03). Thus, the scope of claim 1 is limited to this specific peptide.

The Examiner asserts that the data from Figure 1 is not clear and Figure 1 fails to show any correlation between the insulin resistance disease state and the SEQ ID NO:2. The Examiner further asserts that it is not clear how many samples are involved in the experiments or what the "C" labels on the bands represent. The Examiner states that there is no information regarding which band

the SEQ ID NOS correspond with.

Applicants respectfully disagree with all of the Examiner's assertions.

At page 46, lines 7-8 of the instant specification as originally filed, SEQ ID NO:2 is identified as apolipoprotein A-I precursor protein having a molecular weight of about 1189 daltons. The description of Figure 3 at page 37 indicates that the spectrum depicted in the figure is that of ion 1189; SEQ ID NO:2. In the photograph of the gel in Figure 1 there is a band labeled Band 7 present in a sample resolved from an insulin resistance patient. This Band 7 has a label "apolipoprotein A-I" indicating that this protein, i.e. the claimed marker, was resolved from this Band 7 (from a sample obtained from an insulin resistance patient). Thus, contrary to the Examiner's assertion, it is clear that SEQ ID NO:2 corresponds to Band 7 as shown in Figure 1.

The gel shown in Figure 1 has 9 lanes: lanes 1-4 (as read from the left) contain samples obtained from patients determined to be normal with regard to insulin resistance; lanes 5-8 contain samples obtained from insulin resistance patients and lane 9 contains a molecular weight standard. The lanes are clearly identified by the terms "normal" and "IR" at the top of the photograph. Thus, contrary to the Examiner's assertion it is clear how many samples are involved in the experiment represented by the gel of Figure 1.

The "C" number labels point out specific bands resolved on the gel, however, none of the C bands are identified with protein names, molecular weights or SEQ ID NOS and thus are not relevant to the currently claimed invention.

Figure 1 demonstrates that the biopolymer marker (SEQ ID NO:2; band 7) is present in body fluid samples obtained from insulin resistance patients, but is not present in body fluid samples obtained from patients determined to be normal with regard to insulin resistance. Thus, a difference is seen between two comparable samples, suggesting that the differentially expressed peptide is linked to insulin resistance.

The specification, as originally filed, does provide a precise protocol on how to analyze the data obtained from the disclosed method. Page 25, line 16 to page 26, line 2 of the instant specification discloses a general outline of how to analyze the data obtained by carrying out the disclosed methods. Page 26, lines 6-13 of the instant specification further describes how samples were compared to develop data and indicates how biopolymer marker peptides were selected as notable sequences. This passage of the instant specification also discloses how certain peptides were selected from a plurality of molecules found within a sample and how peptides were deemed evidentiary of a disease state. Page 5, lines 12-20 also describes how biopolymer markers are evaluated

according to the methods of the instant invention. Page 46, line 23 to page 47, line 2 of the instant specification clearly states the steps of the invention include obtaining a sample from a patient and conducting an MS analysis (mass spectrometry) on the sample. Mass spectrometry is commonly practiced and one of skill in the art would know how to analyze and obtain information from mass spectrometry profiles. It is clear that the data presented in the instant specification was obtained by carrying out mass spectrometry. Thus, Applicants assert that the specification, as originally filed, provides a precise protocol on how to analyze the data obtained by the disclosed protocol.

Additionally, Applicants respectfully submit that such protocols are common practice in the field of proteomics. For example, Scott D. Patterson presents the state of the art in mass spectrometry/proteomics by summarizing the Asilomar Conference on Mass Spectrometry (see attached article, Physiological Genomics 2:59-65 2000; reference 2). This conference took place in 2000, thus coinciding with the time that the instant inventors were working to develop the instant invention.

In the disclosed method of the instant invention, proteins (as seen on a gel) that are identified as differentially expressed between a disease and a non-disease state are selected for excision (from the gel) and identification (see, for example, page 38, lines

7-11 of the instant specification as originally filed, and Figure 1). Such selection methods are common practice in the search for biomarkers of specific physiological states. For example, at page 61, right column of Patterson, several automation processes are discussed in the section titled "Automated identification of gel-separated proteins by mass spectrometry". This discussion begins with the following statement:

"Following quantitative analysis of 2-DE patterns, the next step is the identification of all protein spots that display differential expression."

Thus, it is concluded that it is common practice to select potential disease markers by their differential expression between a disease and a non-disease state.

Furthermore, Applicants respectfully submit that many of the methods disclosed in the instant specification are routinely practiced by those of ordinary skill in the art attempting to identify biomarkers of particular physiological states.

For example, at page 64, left column of Patterson is a description of the SELDI approach (as discussed at the conference by Scot Weinberger) wherein defined chemical/biochemical surfaces are utilized to allow fractionation of proteins from biological fluids in a reproducible manner. This reproducibility allows comparisons between different samples to be made. Weinberger

described a search for markers of benign prostate hyperplasia that, like prostate cancer, displays elevated prostate specific antigen (PSA) levels. The fraction exhibiting a difference between these samples was able to be enzymatically digested, and a number of peptides were generated. These peptides were able to be fragmented using the MALDI-Qq-TOF(a procedure described by Ken Standing at the conference, page 62, left column of Patterson). It was found that there appears to be a difference in the relative level of seminogelin fragments between these two states (prostate cancer and benign prostatic hyperplasia), thus providing a potential differential marker.

Applicants respectfully draw the Examiner's attention to the fact that the method described by Weinberger is analogous to the method described in the instant specification. Furthermore, when interpreting data Weinberger uses the same approach to interpretation as the instant inventors in order to identify seminogelin fragments as a potential marker to distinguish between benign prostate hyperplasia and prostate cancer based on differential expression of the fragments. Additionally, Applicants respectfully point out to the Examiner that Weinberger linked differential expression of seminogelin to benign prostate hyperplasia and prostate cancer without analysis of a sample from a control patient free of disease or analysis of a sample from a

patient having another disease, which is not benign prostate hyperplasia or prostate cancer. Such linking of markers with disease through differential expression is commonly practiced in proteomics.

Furthermore, Applicants assert that those of skill in the art are both highly knowledgeable and skilled and it is obvious that no undue experimentation would be required for a skilled artisan to follow any of the electrophoretic, chromatographic and mass spectrometric protocols presented in the instant specification in order to use the claimed invention. One of skill in the art would be able to view a gel, such as that shown in Figure 1 from which the claimed peptide was identified (SEQ ID NO:2), and recognize a difference between two comparable samples (disease state vs. non-disease state) and further recognize that the peptides present within the gel are differentially expressed between the two sample types.

The data presented in the figures, derived from the working examples established at the time of filing, discloses that the claimed peptide (SEQ ID NO:2) is differentially expressed between insulin resistance and a normal physiological state, thus it can be reasonably predicted that such peptide is linked to insulin resistance. Furthermore, the figures identify SEQ ID NO:2 and the specification discloses how such a sequence was identified as a

notable sequence in relation to insulin resistance.

Thus, Applicants contend a skilled practitioner would find that the data presented in the instant specification is convincing with regard to a link between the claimed biopolymer marker peptide (SEQ ID NO:2) and insulin resistance.

Considering the above comments, it is clear that both the specification and the prior art disclose how to make and use the instant invention. Accordingly, Applicants respectfully contend that the instant invention satisfies the "test for enablement" since one skilled in the art could make or use the invention from the disclosures in the specification coupled with information known in the prior art without undue experimentation.

The Examiner asserts that Applicants have not set forth any supporting evidence that suggests that SEQ ID NO:2 is a unique molecular marker for insulin resistance or any other disease and cites references which allegedly teach that disease markers are highly unpredictable and require extensive experimentation.

The guidelines for a "test of enablement" indicate that if a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 USC 112, is satisfied (see MPEP 2164.01(c)).

Additionally, it has been established that the mere fact that

something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it (see MPEP 2164.02).

Applicants assert that SEQ ID NO:2 is linked to insulin resistance, however, do not claim that SEQ ID NO:2 is a unique marker for any particular disease or condition.

Although the prior art does not specifically recognize that the claimed marker consisting of SEQ ID NO:2, a fragment of the apolipoprotein A-I precursor protein, is related to insulin resistance, it does recognize that the plasma lipid profile is modified in insulin resistance and diabetes (see attached abstracts of Rigoli et al. Acta Diabetol 32(4):251-256 1995, reference 3 and Berthezene F. Atherosclerosis 124 Supplement:S39-42 1996, reference 4). When one of skill in the art observes differential expression of the claimed peptide between insulin resistance patients and patients determined to be normal with regard to insulin resistance; one of skill in the art will connect this peptide with potential diagnostics and/or therapeutics for insulin resistance (see above discussion of the Patterson reference).

Thus, Applicants respectfully submit that since the specification demonstrates a link between the claimed peptide (SEQ ID NO:2) and insulin resistance and that this link connotes the use of the claimed peptide in potential diagnostics and/or therapeutics

of insulin resistance, the requirement of "how to use" under 35 USC 112, first paragraph is satisfied.

Furthermore, Applicants respectfully submit that one of ordinary skill in the art would find the suggestion of a link between the claimed peptide (SEQ ID NO:2) and insulin resistance to be reasonable.

At page 46, of the instant specification as originally filed, SEQ ID NO:2 is identified as a fragment of apolipoprotein A-I precursor protein. As mentioned above, the plasma lipid profile is modified in insulin resistance (see references 3 and 4). Specifically, it is known that the fractional catabolic rate of apolipoprotein A-I is increased in insulin resistance and diabetes (see attached abstract of Duvillard et al. Atherosclerosis 152(1):229-237 2000; reference 5). Furthermore, it is possible to have an increase in the number of glycosylated apolipoprotein A-I molecules in insulin resistance and diabetes (see reference 4). One of ordinary skill in the art, considering the known involvement of apolipoprotein A-I with insulin resistance, upon observation of the differential expression of SEQ ID NO:2 in insulin resistance versus normal control, would find it reasonable to believe that this peptide is related and/or linked to insulin resistance.

Therefore, one of ordinary skill in the art would recognize the linkage between SEQ ID NO:2, apolipoprotein A-I and insulin

resistance and thus would also find the suggestion of SEQ ID NO:2 as a marker for insulin resistance entirely reasonable.

The Examiner cites two articles; Tascilar *et al.* (see attached abstract, Annals of Oncology 10, Supplement 4:S107-S110 1999; reference 6) and Tockman *et al.* (see attached abstract, Cancer Research 52:2711s-2718s 1992; reference 7) which are allegedly relevant to the instant invention.

According to the Examiner, Tascilar *et al.* is an article published in an oncogenic journal reporting on diagnostic methods in the realm of disease states. The Examiner appears to have drawn a direct parallel between the diagnostic methods reported by Tascilar *et al.* and the diagnostic methods of the instant invention. The Examiner then cites two fragmented quotations from Tascilar *et al.* "...these tests should be interpreted with caution..." and "the genetic changes found in sources other than the pancreas itself (blood, stool) should be evaluated prudently". The Examiner appears to be commenting on the predictability of molecular-based assays.

Applicants respectfully disagree with the Examiner's reliance on the article by Tascilar et al.

Applicants assert that the claimed peptide (SEQ ID NO:2) is linked to insulin resistance; a statement which is enabled by the description of methods as set forth in the specification and by

data presented in Figures 1 and 3. Thus, applicants respectfully submit that the claimed method involves a simple observation of the levels of expression of SEQ ID NO:2 (as shown in Figure 1) and does not require any other evaluation of genetic changes in the organism in which the sequence is observed.

Furthermore, the study of Tascilar et al. is concerned with the evaluation of samples for genetic mutations (K-ras and p53 mutations) for early detection of pancreatic cancer (see attached abstract of Tascilar et al. Annals of Oncology 10, Supplement 4:S107-S110 1999; reference 6). It appears that Tascilar et al. suggest that protein markers may be useful for early detection of pancreatic cancer; however there does not seem to be any other reference to protein markers, thus the study of the instant inventors (drawn to protein markers and not to genetic markers) is not analogous to the study of Tascilar et al.

Accordingly, Applicants respectfully submit that the Tascilar *et al.* article is not relevant to the instant invention.

Similarly, the Examiner cites another article, Tockman *et al* (Cancer Research Supplement 52:2711s-2718s 1992; reference 7) which is deemed to teach conditions necessary for a suspected cancer biomarker (intermediate end point marker) to have efficacy and success in a clinical application. The reference is drawn to biomarkers for early lung cancer detection, however the basic

principles are applicable to other oncogenic disorders, according to the Examiner. Tockman *et al* is deemed to teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials. Early stage markers of carcinogenesis have clear biological plausiblity as markers of pre-clinical cancer if validated to a known cancer outcome. According to the Examiner, Tockman *et al* reiterates that the predictability of the art in regards to cancer prognosis and the estimation of life experience within a population with a disease or disorder are highly speculative and unpredictable.

Tockman *et al* is deemed to teach that the essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical disease and link those marker results with histological confirmation of disease.

Applicants respectfully disagree with the Examiner's reliance on the article by Tockman et al.

The Tockman *et al* article is concerned with early detection of lung cancer biomarkers and apparently does not discuss biomarkers for insulin resistance or diabetes.

Tockman et al. link several biopolymer markers to lung cancer in a manner analogous to that of the instant specification. Tockman et al. state at page 2712s, left column:

"A functional membrane-associated bombesin receptor recently has been isolated from human small cell lung carcinoma (NCI-H345) cells (23), and bombesin-like peptides have been found in the bronchial lavage fluid of asymptomatic cigarette smokers (24). Thus markers of growth factor expression, insofar as they reflect oncogene activation, may also hold promise for the detection of early (preneoplastic) lung cancer."

From this statement, it is clearly evident that Tockman et al. link bombesin with small cell lung cancer and associate it with potential diagnostics for small cell lung cancer. It does not appear that bombesin was "validated" and/or subjected to any "criteria" prior to this association.

Additionally, Tockman et al. state at page 2713s, left column:

"Evidence of a transformed genome, by expression of tumor-associated antigens, oncofetal growth factors, or specific chromosomal deletions has clear biological plausibility as a marker of preclinical lung cancer."

From this statement, it appears that Tockman et al. believe that the expression of certain proteins provides evidence of a transformed genome and since this transformed genome is associated

with lung cancer, it is reasonable to believe that these certain proteins are potential markers.

Such parallel reasoning between Tockman et al. and the instant specification, further supports Applicants contention that one of ordinary skill in the art would not have any difficulty seeing a link between the claimed biopolymer marker peptide (SEQ ID NO:2) and insulin resistance.

It is noted that in chemical and biotechnical applications, evidence actually submitted to the FDA to obtain approval for clinical trials may be submitted to support enablement of an invention. However, considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled (see *Scott v. Finney* 32 USPQ 2d 1115 and MPEP 2164.05)

The Examiner is reminded that the considerations made by the PTO involving clinical trials are less stringent than the considerations made by the FDA. Evidence presented by applicant to provide enablement of an invention need only be convincing to one of skill in the art and not conclusive. Thus, Applicants respectfully submit that compliance with the "criteria" of Tockman et al. is not necessary in order to show that the instant invention is enabled.

In conclusion, Applicants claim that the differential

expression of SEQ ID NO:2 between insulin resistance patients and patients determined to be normal with regard to insulin resistance evidences a link between the claimed peptide (SEQ ID NO:2) and insulin resistance; a statement which is enabled by the instant specification, as evidenced by the arguments presented herein. Applicants assert that one of ordinary skill in the art when reviewing the instant specification, given the level of knowledge and skill in the art, would recognize the link between the claimed biopolymer marker (SEQ ID NO:2) and insulin resistance and would further recognize how to use the claimed peptide (SEQ ID NO:2) as a marker for insulin resistance. Thus, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendments to the specification and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

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